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SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: a systematic review and meta-analysis.

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Abstract

Background Sodium–glucose co-transporter 2 (SGLT2) inhibitors may have renal protective effects in people with impaired kidney function. We assessed the use of SGLT2 inhibitors in people with type 2 diabetes with or without renal impairment [defined as estimated glomerular filtration rate (eGFR) of ≥ 30 and < 60 ml/min/1.73 m^2 and/or UACR > 300 and ≤ 5000 mg/g] by conducting a systematic review and meta-analysis of available studies.

Methods Randomised controlled trials (RCTs) were identified from MEDLINE, EMABASE, Web of Science, the Cochrane Library, and search of bibliographies to March 2017. No relevant observational study was identified. Summary measures were presented as mean differences and narrative synthesis performed for studies that could not be pooled.

Results 42 articles which included 40 RCTs comprising 29,954 patients were included. In populations with renal impairment, SGLT2 inhibition compared with placebo was consistently associated with an initial decrease in eGFR followed by an increase and return to baseline levels. In pooled analysis of 17 studies in populations without renal impairment, there was no significant change in eGFR comparing SGLT2 inhibitors with placebo (mean difference, 0.51 ml/min/1.73 m^2; 95% CI: -0.69, 1.72; p=403). SGLT2 inhibition relative to placebo was associated with preservation in serum creatine levels or initial increases followed by return to baseline levels in patients with renal impairment, but levels were preserved in patients without renal impairment. In populations with or without renal impairment, SGLT2 inhibitors (particularly canagliflozin and empagliflozin) compared with placebo were associated with decreased urine albumin, improved albuminiuria, slowed progression to macroalbuminuria, and reduced the risk of worsening renal impairment, the initiation of kidney transplant, and death from renal disease.

Conclusions Emerging data suggests that with SGLT2 inhibition, renal function seems to be preserved in people with diabetes with or without renal impairment. Furthermore, SGLT2 inhibition prevents further renal function deterioration and death from kidney disease in these patients.

Keywords: SGLT2 inhibitor, type 2 diabetes, renal impairment

Introduction

There is a large and growing burden of diabetes globally. In 2013, 382 million people had diabetes and this number has been projected to increase to 592 million by 2035.[1] With increasing life expectancy and prevalence of type 2 diabetes, complications and deaths attributable to diabetes will also increase, especially if there is no concomitant improvement in the health system for its early management.[1] Chronic kidney disease (CKD) is a common complication in people with type 2 diabetes[2] and may in some cases progress to end-stage renal disease, which requires dialysis and/or kidney transplant which are associated with high healthcare costs.[3-5] Indeed, a recent population-based study showed that the costs associated with the treatment of end-stage renal disease in patients with type 2 diabetes was ten times that of type 2 diabetes patients without renal failure.[5]

The kidneys are involved not just in the pharmacokinetic processing of many antidiabetic agents,[6-9] but also in the mechanisms of action of some classes of antidiabetic drugs.[10] Therefore, prescribing antidiabetic drugs in patients with diabetes and CKD can be very challenging, with special concerns regarding safety and efficacy and the need for appropriate dosage adjustment according to the renal function. For patients with type 2 diabetes and CKD, there are limited treatment options for glycaemic control.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, are novel therapeutic agents for the treatment of type 2 diabetes and work by inhibiting glucose reabsorption and induce excretion of glucose in the urine, thereby reducing circulating plasma glucose levels.[11] Their mechanisms of action are independent of insulin action or beta-cell function and their use is associated with reductions in HbA1c levels, weight and systolic blood pressure.[10] Data from phase III trials suggest that SGLT2 inhibitors might achieve their beneficial effects without having significant adverse effects. Treatment with canagliflozin was shown to be associated with decreased albuminuria and an early decrease in estimated glomerular filtration rate (eGFR).[12,13] Yale and colleagues reported that a lower proportion of participants in the canagliflozin 100 and 300 mg groups progressed from normoalbuminuria to micro- or macro-albuminuria, or from micro- to macro-albuminuria compared with those in the placebo group.[13] In the CANagliflozin CardioVascular Assessment Study (CANVAS), there were significant reductions in albuminuria and the albumin-to-creatinine ratio for canagliflozin 100 mg and

300 mg doses, compared with placebo.[12] For nearly 2 decades, the use of Renin-Angiotensin-Aldosterone system (RAAS) inhibition has been employed in the management of diabetes to reduce the rate of progression of diabetes nephropathy.[14,15] The kidney plays a key role in modulating glucose levels by mediating the reabsorption of glucose back into the plasma, after filtration of the blood. Similarly, SGLT2-inhibitors cause vaso-constriction of the afferent arterioles, thus decreasing the hyper-filtration in the glomerulus. This then can lead to a decrease in the rate of progression of proteinuria.[8] These new type 2 diabetes drugs may therefore offer an alternative option for renal protection. Since the mechanism of renal protection of SGLT2 inhibitors seems to occur independently of their glycaemic controlling effect, it is plausible that their effect on prevention of deterioration of renal function could be maintained; even when they are used in patients with impaired renal function, where they are usually deemed not to be effective for glucose control. Currently SLGT2 inhibitors are only licenced for use in glycaemic control and hence contra-indicated in people with eGFR less than 45 ml/min/1.73 m^2. In the absence of treatment options for the prevention of deterioration of renal impairment other than RAAS inhibition, the use of SGLT2 inhibitors show some promise in this area. To our knowledge, the only RCT designed to assess whether an SGLT2 inhibitor compared with a placebo, has a renal protective effect in participants with type 2 diabetes mellitus, chronic kidney disease and macroalbuminuria, is the **"**Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) study". However, this study is not due to be completed until 2019. (ClinicalTrials.gov Identifier: NCT02065791). There are currently no systematic reviews or meta-analysis of RCTs on this subject. In this context, we aimed to pool available interventional evidence in one updated systematic meta-analysis. Our aim was to determine if the use of SGLT2 inhibition prevents further renal function deterioration in people with type 2 diabetes with or without renal impairment.

Methods

Data sources and search strategy

This review was conducted using a predefined protocol and in accordance with PRISMA (**Appendices 1**). We sought studies published before March 06, 2017 (date last searched) using

MEDLINE, EMBASE, Web of Science, and the Cochrane electronic databases. The computer-based searches combined terms related to the intervention (e.g., *SGLT2 inhibitors, dapagliflozin, canagliflozin, empagliflozin*); population (e.g., *type 2 diabetes, renal impairment, CKD, renal insufficiency*); and outcomes (e.g., *serum creatinine, urine albumin-to-creatinine ratio*) in humans, without any language restriction. Details on the search strategy are provided in **Appendix 3**. Two authors working independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full texts were retrieved from studies that satisfied all selection criteria. Bibliographies of selected studies and relevant reviews identified on the topic area were manually scanned for additional publications.

Study selection and eligibility criteria

Intervention studies were eligible if they were randomised controlled, open or blinded, or non-randomised trials; that assessed the effects of SGLT2 inhibitor treatment compared with a placebo or standard care in adults with type 2 diabetes with or without renal impairment and reported renal outcomes [as assessed by eGFR, blood urea nitrogen (BUN), serum creatinine, urine albumin-to-creatinine ratio (UACR), and urine albumin or changes in the concentrations of these markers] in adults (≥ 18 years old) with type 2 diabetes with or without renal impairment (defined as eGFR of ≥ 30 and < 60 ml/min/1.73 m^2 and/or UACR > 300 and ≤ 5000 mg/g). Studies were excluded if they (i) specifically enrolled only patients with known renal insufficiency or established renal parenchymal disease without diabetes mellitus; (ii) recruited patients with a history of diabetic ketoacidosis, type 1 diabetes mellitus, history of hereditary glucose-galactose malabsorption, primary renal glucosuria, or renal disease that required treatment with immunosuppressive; (iii) cross-sectional designs.

Data extraction

Two authors (SKK and SS) used a predesigned data extraction form to independently extract data and a consensus was reached in case of any inconsistency with involvement of a third (KK). Relevant information was extracted on study design; publication year, study year, baseline population including proportion of men; geographical location; average age at baseline; numbers enrolled and randomised;

allocation concealment; blinding; type of SGLT2 inhibitor and dosage; duration of treatment or follow-up; treatment comparisons; and nature of outcome and numbers. We extracted summary measures and risk estimates reported for fully-adjusted models, where relevant. In the case of multiple publications involving the same study, the most up-to-date or comprehensive information was abstracted.

Assessing the risk of bias

The Cochrane Collaboration's risk of bias tool[16] was used to assess the quality of the included trials. This tool evaluates seven possible sources of bias which are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each individual component, studies were classified into low, unclear and high risk of bias.

Statistical analysis

Summary measures were presented as mean differences for continuous outcomes and risk estimates for categorical outcomes, where relevant. For data reported as medians, ranges, and 95% confidence intervals (CIs), means and standard deviations were calculated as described by Hozo and colleagues. [17] The inverse variance weighted method was used to combine summary measures using random-effects models to minimise the effect of between-study heterogeneity [18]. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic; and was distinguished as low ($I^2 \geq 25\%$), moderate ($25\% < I^2 \geq 50\%$) or high ($I^2 \geq 75\%$).[19] Given the variety of measures reported for renal outcomes and inconsistent reporting by some of the trials, a formal meta-analysis could not be performed for some of the data. A narrative synthesis was performed for studies that could not be pooled. The findings of such studies were summarised in tables that included the main characteristics of the study and the results in natural units as reported by the investigators. All tests were two-tailed and p-values of 0.05 or less were considered significant. STATA release 13 (Stata Corp, College Station, Texas, USA) was used for all statistical analyses.

Results

Study identification and selection

Figure 1 shows the flow of studies through the review. The search of relevant databases and manual scanning of reference lists of relevant studies identified 1171 potentially relevant articles. After the initial screening of which was based on titles and abstracts, 119 articles remained for full text evaluation. Following detailed evaluation, 77 articles were excluded because (i) they were based on reviews (n=32); (ii) the outcomes reported were not relevant (n=29); (iii) included populations not relevant to review (n=12); and (iv) duplicate studies (n=4). The remaining 42 articles met the inclusion criteria and were included in the review.

Study characteristics and quality

The 42 articles included in the review involved a total of 40 RCTs comprising 29,954 participants[13,20-60] (**Table 1**). All 40 trials were conducted in populations with type 2 diabetes; however, 6 trials were based in populations who also had impaired kidney function or prevalent kidney disease (n=2,768), whilst 37 trials were conducted in populations not specifically diagnosed with kidney disease. Four articles were based on two trials which reported results for different time periods.[13,20,43,44] All included studies were double-blinded RCTs; however, majority of trials extended treatment in an open-label manner after the initial double-blind phase. Except for three trials that were specifically conducted in Japan or Finland, all the other trials were conducted in multiple countries. The type of SGLT2 inhibitors used included dapagliflozin, canagliflozin, and empagliflozin. Luseogliflozin, ipragliflozin, and tofogliflozin which are SGLT2 inhibitors developed and approved in Japan, were employed by some of the trials conducted in Japan. The treatment duration ranged from 24 weeks to 2.6 years. Using the Cochrane Collaboration tool, all trials demonstrated low risk of bias in the areas of random sequence generation and blinding of participants & personnel, whiles majority of trials demonstrated an unclear risk of bias in the area of blinding of outcome assessments. (**Appendix 3**).

Change in estimated GFR

Populations with renal impairment In three studies (n=478),[22-24] reductions in eGFR levels were seen with SGLT2 inhibitors relative to placebo during the first few weeks of treatment, but the levels increased thereafter and returned towards baseline values by the end of treatment period. In the 26-week, double-blind, core treatment trial phase of the 52-week study by Yale and colleagues,[13] decreases in eGFR from baseline were observed for all treatment groups. However, the reductions were larger in the canagliflozin 100 and 300 mg groups compared with the placebo group (least square percent mean change, -9.1% versus -10.1% versus -4.5% respectively). The decreases in eGFR with canagliflozin treatment were substantial during the first weeks of treatment and then trended towards baseline values at the end of the 26-week treatment period. In the article that reported study findings over the entire 52 weeks of treatment, eGFR levels returned to baseline values at the end of 52 weeks.[20]

Populations without renal impairment In pooled analysis of 17 studies, there was no significant change in eGFR comparing SGLT2 inhibitors with placebo (mean difference, 0.51 ml/min/1.73 m^2; 95% CI: -0.69, 1.72; p=403). There was evidence of substantial heterogeneity between contributing studies I^2=75% (60, 84%; p<0.001) (**Figure 2**). On exclusion of the study that reported imprecise estimates (very wide 95% CIs),[50] the finding was similar (mean difference, 0.46 ml/min/1.73 m^2; 95% CI: -0.75, 1.66; p=459) and evidence of substantial heterogeneity remained I^2=76% (62, 85%; p<0.001). In a subgroup analysis by the class of SGLT2 inhibitors, no significant change was observed in eGFR for any of the SGLT2 inhibitors evaluated (**Figure 3**). In pooled analysis of two studies that reported estimates as mean percent changes,[28,37] 100 mg of canagliflozin compared with placebo was not associated with a significant change in eGFR (mean percent difference, -1.11; 95% CI: -2.97, 0.75; p=242). In the 12-week double-blind, three-arm parallel-group, placebo-controlled trial by Wilding and colleagues,[30] only minor changes were observed in eGFR at the end of treatment (mean change, -0.84, 1.45, and -0.58 ml/min/1.73 m^2 for 10 mg dapagliflozin, 20 mg dapagliflozin, and placebo groups respectively). In the 52-week randomised, double-blind, phase III non-inferiority trial that compared canagliflozin with glimepiride in patients with type 2 diabetes inadequately

controlled with metformin (CANTATA-SU),[38] decreases in eGFR were marked for glimepiride compared with 100 mg and 200 mg of canagliflozin (mean change, -5.1, -1.7, and -3.0 ml/min/1.73 m^2 respectively). In the trial of dapagliflozin versus glipizide in patients with type 2 diabetes inadequately controlled with metformin monotherapy,[55] the decrease in eGFR was more dramatic for glipizide compared with dapagliflozin at the end of 52 weeks therapy (mean change, -5.4 and -0.5 ml/min/1.73 m^2 respectively) (**Table 2**).

Change in BUN

Populations with renal impairment In pooled analysis of two studies (n=226), a significant increase in BUN was seen with SGLT2 inhibitors compared with placebo (mean difference, 2.06 mg/dl; 95% CI: 0.88, 3.25; p=0.001).[22,24] However, in the initial 24 week trial by Haneda and colleagues[22] to evaluate the efficacy and safety of luseogliflozin compared to placebo in patients with moderate renal impairment, BUN levels increased until week 12 and remained stable thereafter. Yale and colleagues also showed canagliflozin 100 and 300 mg to be associated with increases in BUN relative to placebo at the end of the 52 week period (least square percent mean change, 12% versus 17.3% versus 5.4% respectively).[20]

Populations without renal impairment Pooled analysis of seven studies (n=1039) showed a significant increase in BUN when SGLT2 inhibitors were compared with placebo (mean difference, 1.80 mg/dl; 95% CI: 1.37, 2.24; p<0.001) (**Figure 4**). In the 16-week placebo-controlled trial by Kashiwagi and colleagues to assess the efficacy and safety of 50 mg ipragliflozin as monotherapy in Japanese patients;[39] though there was an increase in BUN associated with ipragliflozin treatment, the increase was not dependent on duration of treatment and the levels returned to almost baseline levels during the 4-week follow-up period after completion of treatment. There was no evidence of substantial heterogeneity between contributing studies I^2=7% (0, 73%; p=0.373). In pooled analysis of five studies that reported BUN in mmol/l,[32-36] 10 mg dapagliflozin compared with placebo was associated with a significant increase in BUN (mean difference, 0.48 mmol/l; 95% CI: 0.32, 0.64; p<0.001). There was no evidence of heterogeneity between contributing studies I^2=0% (0, 79%; p=0.432). In pooled analysis of five studies that reported estimates as mean percent changes,[27,28,37,46,47]

100 mg of canagliflozin compared with placebo was associated with a significant increase in BUN (mean percent difference, 11.00; 95% CI: -6.51, 15.50; $p<0.001$). There was evidence of heterogeneity between contributing studies $I^2=66\%$ (12, 87%; $p=0.018$). **Table 2** reports changes in BUN for trials that could not be pooled. When canagliflozin was compared with glimepiride in the CANTATA-SU trial,[38] increases in BUN were noted with canagliflozin compared with glimepiride (mean percent change, 15.3, 22.0, and 6.50 for 100 mg canagliflozin, 300 canagliflozin, and glimepiride respectively). Seino and colleagues in their trial of luseogliflozin monotherapy at doses of up to 10 mg in Japanese patients with type 2 diabetes,[52] demonstrated increases in BUN in the 1 and 10 mg groups compared with placebo. In another trial by the same authors, 2.5 mg luseogliflozin compared with placebo was associated with a significant increase in BUN.[53] Nauck and colleagues demonstrated increased mean values of BUN with dapagliflozin treatment compared with glipizide in patients with type 2 diabetes inadequately controlled with metformin monotherapy.[55]

Change in serum creatinine

Populations with renal impairment Treatment with ipragliflozin was associated with increase in serum creatinine levels in the short term, but levels returned to baseline values at the end of the treatment period (mean difference, 0.04 mg/dl; 95% CI: -0.00, 0.08).[24] In a 52-week phase III trial, serum creatinine levels hardly changed with 2.5 mg luseogliflozin treatment (mean difference, 0.04 mg/dl; 95% CI: 0.00, 0.07).[22] In another trial, an increase in serum creatinine level was observed in the first week with dapagliflozin treatment (mean difference, 0.03 mg/dl; 95% CI: -0.09, 0.14), but this increase remained stable during the remainder of the study.[23] Canagliflozin 100 and 300 mg was shown to be associated with increases in serum creatinine compared with placebo at the end of a 52 week treatment period (least square percent mean change, 6.6% versus 11.2% versus 5.2% respectively).[20]

Populations without renal impairment In pooled analysis of eight studies, there was no significant change in serum creatinine when comparing SGLT2 inhibitors with placebo (mean difference, 0.00 mg/dl; 95% CI: -0.01, 0.01; $p=0.724$) and there was no evidence of substantial heterogeneity between contributing studies $I^2=28\%$ (0, 67%; $p=0.209$) (**Figure 5**). In pooled analysis of six studies that

reported serum creatinine in µmol/l,[32-36,44] 10 mg dapagliflozin or empagliflozin compared with placebo was not associated with a significant change in serum creatinine (mean difference, 0.042 µmol/l; 95% CI: -0.838, 0.922; *p*=926). There was no evidence of heterogeneity between contributing studies I^2=0% (0, 75%; *p*=0.659). In pooled analysis of five studies that reported estimates as mean percent changes,[27,28,37,46,47] 100 mg of canagliflozin compared with placebo was not associated with a significant change in serum creatinine (mean percent difference, 0.068; 95% CI: -1.084, 1.220; *p*=0.908). There was no evidence of heterogeneity between contributing studies I^2=2% (0, 80%; *p*=0.394).

Results of individual trials which could not be pooled are reported in **Table 2**. There were no significant changes in serum creatinine when luseogliflozin at doses of 0.5, 2.5, and 5 mg were compared to placebo.[51] In two other trials by Seino and colleagues, treatment with luseogliflozin compared with placebo was not associated with significant changes in serum creatinine.[52,53] Nauck and colleagues demonstrated no significant change in serum creatinine for dapagliflozin treatment compared with glipizide.[55] No significant change was observed for serum creatinine comparing empagliflozin with glimepiride.[59]

Change in urine albumin-creatinine ratio

Populations with renal impairment **Table 2** reports changes in UACR for trials that reported these outcomes. At the end of a 24 week treatment period, canagliflozin 100 and 300 mg were associated with greater decreases in UACR compared with placebo (median percent reduction, -29.9% versus -20.9% versus -7.5% respectively).[13] At 52 weeks follow-up in the same trial, canagliflozin 100 and 300 mg were still associated with decreases in UACR (median percent change, -16.4% and -28.0% respectively); however, an increase was seen with placebo (median percent change, 19.7%).[20] At 104 weeks, dapagliflozin 5 mg compared with placebo was associated with an increase in UACR from baseline, but this was not statistically significant (mean difference, 8.30 mg/g; 95% CI: -262.4, 279.0; *p*=0.952); whiles dapagliflozin 10 mg compared with placebo decreased UACR from baseline (mean difference, -81.39 mg/g; 95% CI: -412.25, 249.47; *p*=0.632).[23] At the end of a 24 week treatment period, ipragliflozin 50 mg compared with placebo was associated with a decrease in UACR (mean

difference, -55.18 mg/g Cr; 95% CI: -412.25, 249.47; p=0.173).[24] Urine albumin-creatinine ratio improved with 25 mg empagliflozin compared with placebo at week 52 (adjusted mean difference, -183.78; 95% CI: -305.18, -62.38; p=0.0031).[25] In a double-blind phase III trial that compared the efficacy and safety of empagliflozin with glimepiride as add-on to metformin in patients with type 2 diabetes with and without renal impairment, a marked decrease in UACR was observed with empagliflozin, whiles a marked increase was observed with glimepiride in patients with UACR > 300 mg/g at baseline.[59]

Populations without renal impairment In pooled analysis of three trials,[40,41,50] 50 mg ipragliflozin compared with placebo was not associated with a significant change in UACR (mean difference, -2.78 mg/g Cr; 95% CI: -14.79, 9.23; p=0.650). There was no evidence of heterogeneity between contributing studies I^2=0% (0, 90%; p=0.408). Pooled analysis of two trials that reported UACR in mg/g, [34,60] showed no significant change in UACR when comparing dapagliflozin or canagliflozin with placebo (mean difference, -3.28 mg/g; 95% CI: -18.86, 12.30; p=0.680). Results of trials that could not be pooled are reported in **Table 2**. In a phase IIb trial that evaluated the efficacy, safety, tolerability and pharmacokinetics of empagliflozin, mean UACR values decreased from baseline in the intervention and placebo groups.[29] In the CANTATA-SU trial,[38] there were only small changes in UACR values comparing canagliflozin with glimepiride (mean change: -0.9, -0.1, and 0.7 g/mol for 100 mg canagliflozin, 300 canagliflozin, and glimepiride respectively). In a 52-week trial in patients receiving metformin therapy, dapagliflozin treatment dramatically decreased UACR when compared with glipizide.[55] In the double-blind phase III trial that compared the efficacy and safety of empagliflozin with glimepiride as add-on to metformin in patients with type 2 diabetes, no significant change was observed for UACR comparing empagliflozin treatment with that of glimepiride.[59]

Urine albumin

Populations with renal impairment At the end of a 52 week treatment period, canagliflozin 100 and 300 mg were associated with decreases in urine albumin (median percent change, -34.4% and -49.0% respectively); however, an increase was seen with placebo (median percent change, 14.3%).[13] At 24 weeks, luseogliflozin 2.5 mg compared with placebo was associated with a non-significant decrease in

creatinine-corrected urine albumin (mean difference, -25.11 mg/g Cr; 95% CI: -146.50, 96.30; p=0.683).[22] Yale and colleagues evaluated progression of albuminuria from baseline, and showed that a lower proportion of participants in canagliflozin 100 and 300 mg groups progressed compared with placebo (shift from normoalbuminuria to micro or macroalbuminuria/microalbuminuria to macroalbuminuria, 5.1% versus 8.3% versus 11.8% respectively).[13] Similar results were observed when empagliflozin 25 mg was compared with placebo: (shift from no albuminuria to macroalbuminuria, 12.2% versus 22.2%); (shift from microalbuminuria to macroalbuminuria, 2.0% versus 11.4%); (shift from macroalbuminuria to microalbuminuria, 32.6% versus 8.6%); and (shift from microalbuminuria to no albuminuria, 27.5% versus 21.4%).[25]

Populations without renal impairment In the CANVAS trial,[26] there was a reduced risk of the outcome of progression to albuminuria when canagliflozin 100 or 300 mg was compared with placebo (hazard ratio, 0.73; 95% CI, 0.67, 0.79). Canagliflozin 100 or 300 mg compared with placebo was also associated with an increased risk of regression of albuminuria (hazard ratio, 1.70; 95% CI, 1.51, 1.91).

Other outcomes

Populations with renal impairment In the EMPA-REG OUTCOME trial, empaglifozin 10 or 25 mg compared with placebo was associated with a reduced risk of incident or worsening nephropathy (defined as progression to macroalbuminuria, a doubling of the serum creatinine level, accompanied by an eGFR of $\leq$ 45 ml/min/1.73 m^2, the initiation of renal-replacement therapy; or death from renal disease) (hazard ratio, 0.58; 95% CI, 0.47, 0.71; p<0.001). There was also a reduced risk of the composite outcome of a doubling in serum creatinine, initiation of renal replacement therapy, or death due to renal disease; when empaglifozin 10 or 25 mg compared with placebo (hazard ratio, 0.51; 95% CI, 0.31, 0.85; p=0.010).[21]

Populations without renal impairment In the CANVAS trial, canagliflozin 100 or 300 mg compared with placebo was associated with a reduced risk of the composite outcome of sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47, 0.77).[26]

Discussion

Key findings

In this systematic review and meta-analysis from available RCTs, we have compared SGLT2 inhibition with placebo or standard care in people with type 2 diabetes with or without renal impairment and assessed relevant renal outcomes. In the greater majority of trials of type 2 diabetes patients with renal impairment, SGLT2 inhibitors compared with placebo were associated with initial decreases in eGFR during the first few weeks of therapy and there were greater decreases with higher doses compared with lower doses of SGLT2 inhibitors. However, the levels returned to baseline values at the end of the treatment period. For trials of populations without renal impairment, renal function as measured by eGFR seemed to be preserved with SGLT2 inhibitor treatment and this was consistent for the different classes of SGLT2 inhibitors. There were rather dramatic decreases in eGFR when standard antidiabetic drugs such as glimepiride or glipizide were compared with SGLT2 inhibitors. In populations with renal impairment, SGLT2 inhibition was associated with preservation of serum creatinine levels or there were initial increases followed by return to baseline levels. However, in populations without renal impairment, levels of serum creatinine did not change significantly with SGLT2 inhibitor therapy. Evidence from a limited number of studies however showed increases in levels of BUN with SGLT2 treatment compared with placebo in populations with renal impairment. In populations without renal impairment, there were significant increases in BUN with SGLT2 inhibitor treatment. In patients with renal impairment, whereas majority of trials showed decreases in UACR, others showed an increase in UACR; however, majority of the results were not statistically significant. However, based on the statistically significant results from two trials,[13,25] the overall findings suggest that SGLT2 inhibitors (particularly canagliflozin and empagliflozin) compared with placebo are associated with improvement in UACR in populations with renal impairment. The greater majority of trials conducted in populations without renal impairment did not demonstrate any significant changes in UACR with SGLT2 inhibitor treatment, except for one trial which showed a dramatic decrease in UACR with dapagliflozin treatment compared with glipizide.[55] In populations with or without renal impairment, treatment with SGLT2 inhibitors was associated

with decrease in urine albumin levels, slowed progression to macroalbuminuria, and improved albuminuria. Finally, empaglifozin or canagliflozin compared with placebo was associated with a reduced risk of worsening renal impairment, initiation of renal-replacement therapy, or death from renal disease.

Comparison with previous studies

A number of limited reviews have been conducted on the topic and some of our findings concur with the results of these studies. However, our findings which were based on type 2 diabetes patients with or without renal impairment, provide several relevant findings that have not been previously reported. In pooled individual participant data analysis of four RCTs that enrolled patients with type 2 diabetes and stage 3 CKD, canagliflozin 100 and 300 mg decreased eGFR, whiles increases were seen with the placebo.[61] In the same study, canagliflozin 100 and 300 mg compared with placebo showed reductions in albuminuria. In another pooled individual participant data analysis of five RCTs that enrolled patients with type 2 diabetes and prevalent microalbuminuria or macroalbuminuria, empagliflozin compared with placebo significantly decreased UACR values in the macroalbuminuria group.[62] Our findings which were based on a larger number of trials consistently showed initial decreases in levels of eGFR followed by an increase and return to baseline values with SGLT2 inhibition in populations with renal impairment. There was preservation of serum creatinine levels or there were initial increases followed by return to baseline levels with SGLT2 inhibition. However, for populations without renal impairment, eGFR as well as other renal biomarkers such as serum creatine and UACR were preserved with SGLT2 inhibition. Finally, recent results from the EMPA-REG OUTCOME and CANVAS trials indicate that SGLT2 inhibition slows down the progression of albuminuria and worsening kidney impairment, initiation of kidney transplant, and death from kidney disease in type 2 diabetes patients with or without renal impairment.[21,26]

Potential explanation of findings

Sodium–glucose co-transporter 2 inhibitors work by targeting renal tubular glucose reabsorption. Their action is based on the blockage of SGLT2 sodium-glucose cotransporters that are located in the

tubular cells of the proximal convoluted tubule, thereby inducing glucosuria.[63] Although the efficacy of SGLT2 inhibitors is affected by renal function,[23] emerging data indicates that SGLT2 inhibition has a reno-protective effect.[63] In patients with diabetes, there is an increase in the expression of sodium-glucose co-transport receptors in the proximal tubules leading to an increased re-absorption of sodium and glucose in 1:1 stoichiometry in the proximal tubule [3]. This leads to a decreased delivery of sodium to the macular densa. As a result of this, less sodium is available for the breakdown of ATP to produce adenosine which is a potent vasoconstrictor [4]. Therefore, the afferent arteriole will dilate leading to increased pressure and hyper filtration in the glomerulus, which stimulates the cascade of pathophysiological changes that cause diabetes nephropathy. Sodium-glucose linked transporter 2 inhibitors enhance delivery of sodium to the macular densa which leads to increase breakdown of ATP producing adenosine. This then causes vaso-constriction of the afferent arterioles, thus decreasing the hyper-filtration in the glomerulus. This then can lead to a decrease in the rate of progression of proteinuria. The overall evidence shows that SGLT2 inhibition causes reductions in eGFR. However, these reductions are usually seen in the early phases of treatment initiation with levels subsequently returning to normal during treatment. Yale and colleagues showed a reduction in eGFR with canagliflozin therapy in the first weeks of therapy, but the levels returned to normal values over the entire treatment period.[13] Yamout and colleagues in pooled analysis of four trials showed that the declines in eGFR associated with canagliflozin therapy were seen during early treatment initiation; however, these levels returned to baseline values over time.[61] There have been suggestions that these initial reductions in eGFR are related to the volume depletion associated with the diuretic properties of SGLT2 inhibitors. The increase in levels of the blood renal biomarkers therefore reflect this volume depletion.[20]

Implications of findings

In end-stage renal disease (ESRD), the need for Renal Protection Therapy (RRT) can lead to significant deterioration of the patient's quality of life and exerts significant cost on the health system.[64] For the past two decades, clinicians have merely depended on RAAS inhibition as a target for preventing the deterioration of diabetes nephropathy, albeit with some good results. The current

results suggest that SGLT2 inhibitor therapy in diabetes and renal impairment could prevent further renal deterioration. The current evidence suggests that the protective effects of SGLT2 inhibitors could be attributed to canagliflozin and empagliflozin, two of the well-known SGLT2 inhibitors used in clinical practice. Further robust interventional evidence such as those from the ongoing CREDENCE study, may help confirm the reno-protective effect of SGLT2 inhibitor therapy. If this is confirmed, it will be a welcome addition to the limited armamentarium of therapeutic options in this area. Given the high mortality rates associated with CKD and the healthcare costs associated with the management of CKD in patients with type 2 diabetes,[3-5] the potential benefits of SGLT2 inhibitors in reducing the progression of CKD will be useful for clinical practice. In recent years, more and more people with diabetes and its complications such as nephropathy are now managed in primary care and only referred to specialist units for consideration of RRT in the very late stages. The early use of SGLT2 inhibitors in the prevention of renal deterioration in addition to their glycaemic control deserves further study.

Strengths and limitations

Strengths of the current study included clearly defined populations which were based on people with type 2 diabetes and with or without renal impairment. Our review was prespecified to include all observational study designs as well as RCTs published on the topic; therefore our search strategy was very detailed and spanned several databases. We were however unable to identify any relevant observational study that met the inclusion criteria. Our review was comprehensive and to our knowledge included the greater majority of relevant trials published on the topic. An assessment of the methodological quality of included trials were conducted and they were all of adequate quality. In addition, we reported on a wide range of renal outcomes. Some limitations also deserve consideration. Majority of trials included in the review extended treatment in an open-label manner after the initial double-blind core phase, which could have limited the validity of the results. However, majority of these trials reported findings for both phases, results which seemed to follow similar trends. Though we performed quantitative synthesis of the data where possible, inconsistent reporting of outcome measures from some of the studies precluded pooling of all available data. This also prevented us

from conducting subgroup analyses by several relevant clinical characteristics. Due to limited data available, head-to-head comparisons of the different SGLT2 inhibitors could not be explored. There was evidence of substantial between study heterogeneity in some of the analyses and which couldn't be explored because of the limited data. The current findings should stimulate further research on the role of SGLT2 inhibition on renal outcomes in people with diabetes, particularly those with renal impairment.

Conclusions

In conclusion, emerging data suggests that SGLT2 inhibition prevents further renal function deterioration in people with type 2 diabetes with or without renal impairment. In patients with renal impairment, though treatment with SGLT2 inhibitors are associated with reductions in eGFR, the reductions are not substantial and are usually seen in the early phases of treatment initiation, with levels returning to baseline values with time. However, for populations without renal impairment, renal function seems preserved with SGLT2 inhibitors. In populations with or without renal impairment, SGLT2 inhibition is also associated with reduction in UACR, slows down the progression of albuminuria, improves albuminuria, and is also associated with reduced risk of progression to a doubling of the serum creatinine levels, initiation of kidney transplant, and death from kidney disease

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Figure 1. Selection of studies included in the meta-analysis

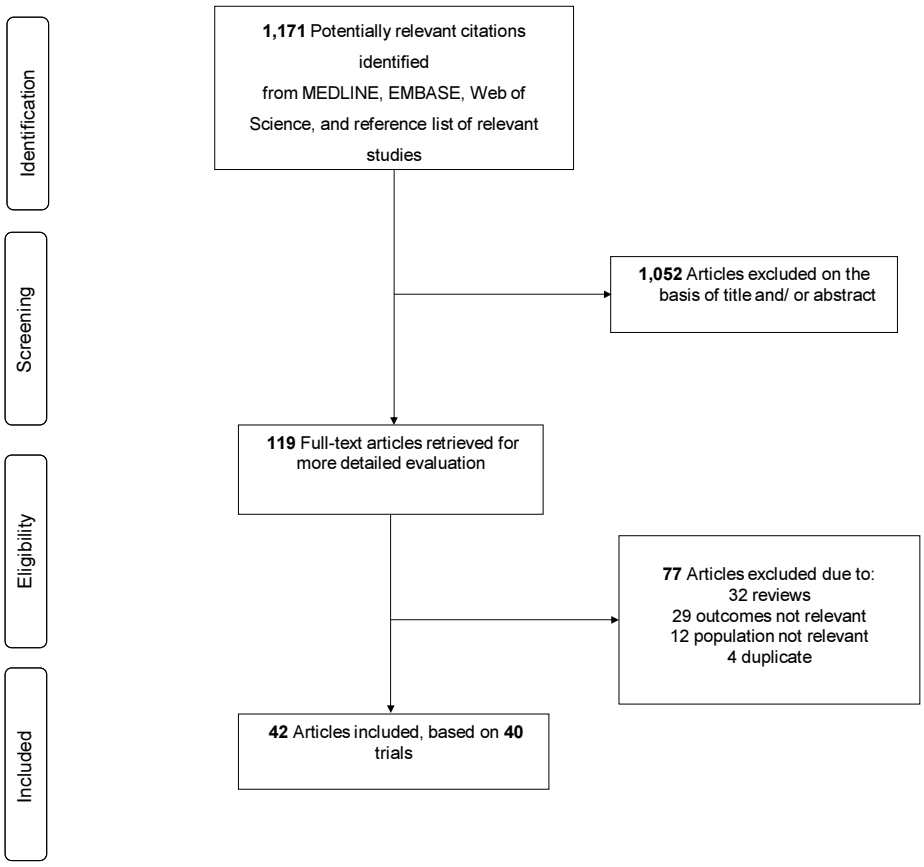
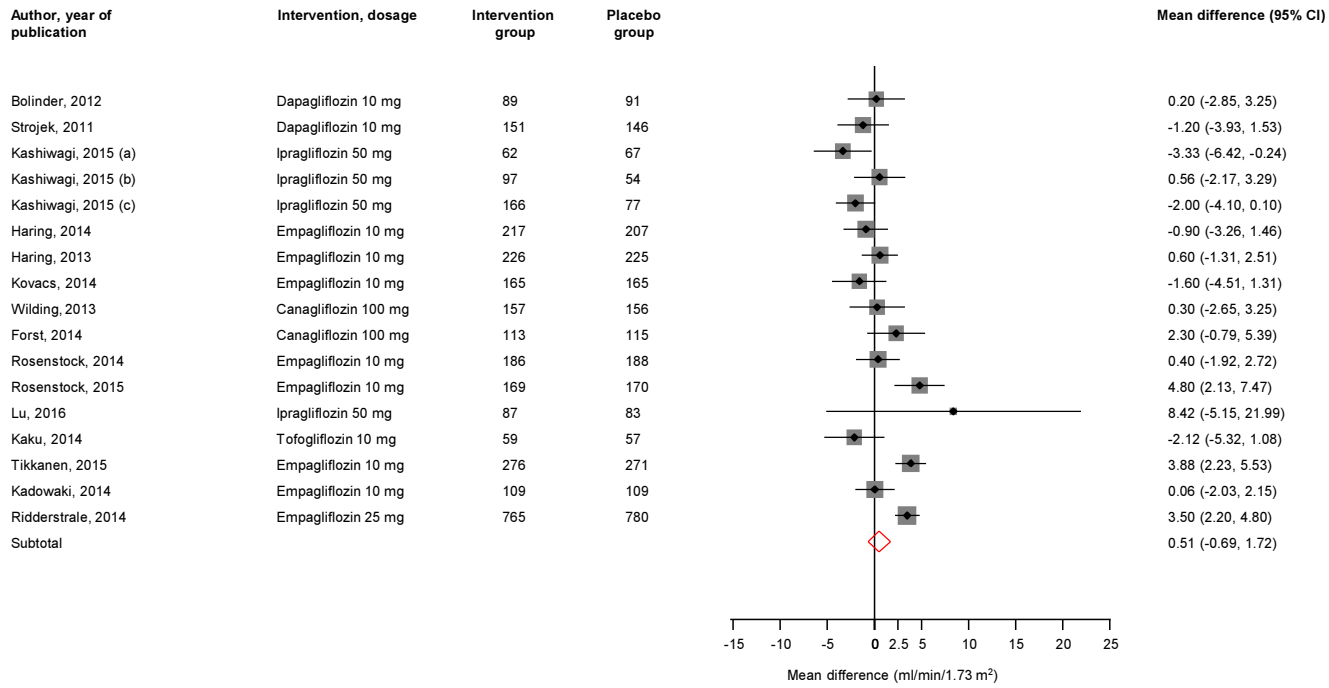
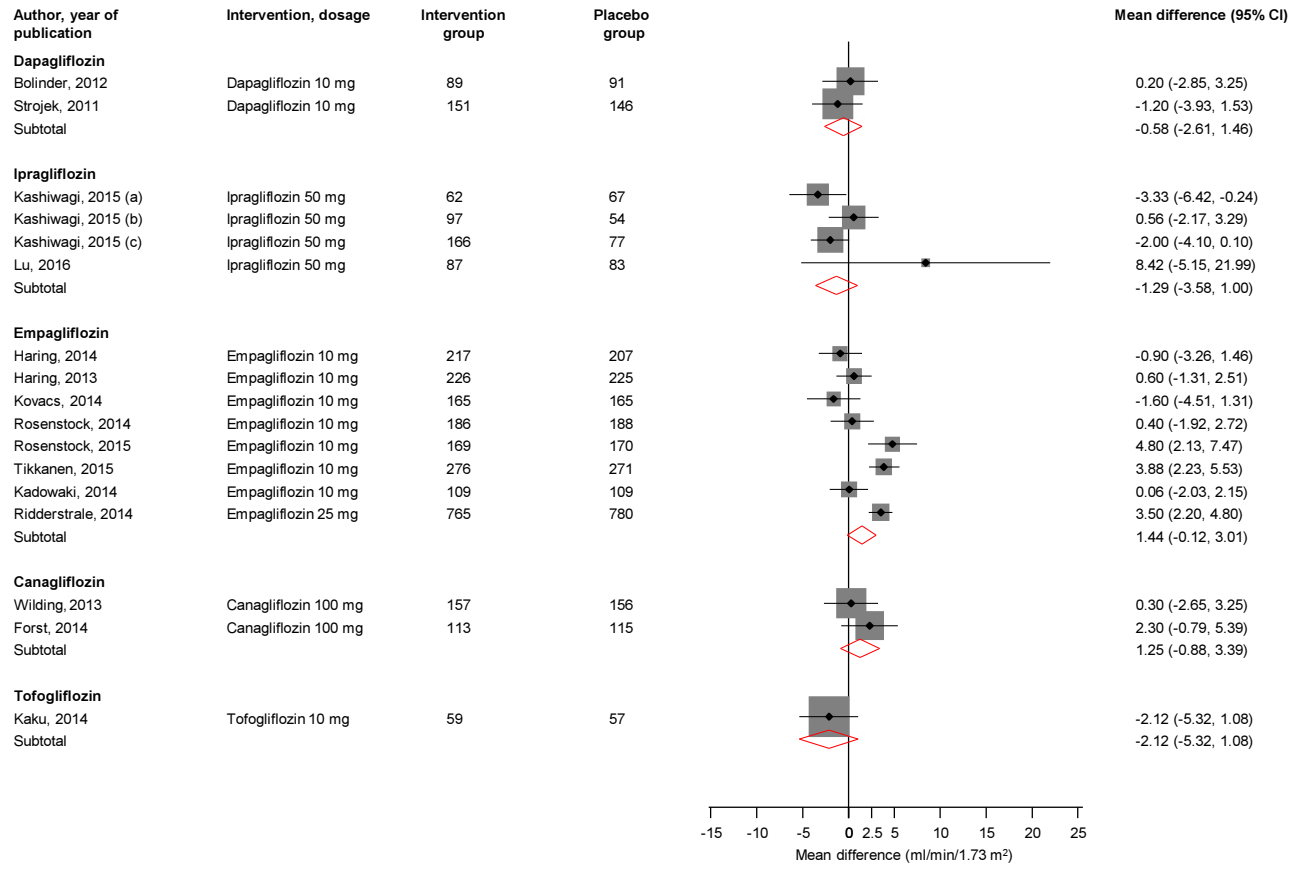


Figure 2. Mean difference in estimated glomerular filtration levels comparing SGLT2 inhibition with placebo in populations without renal impairment



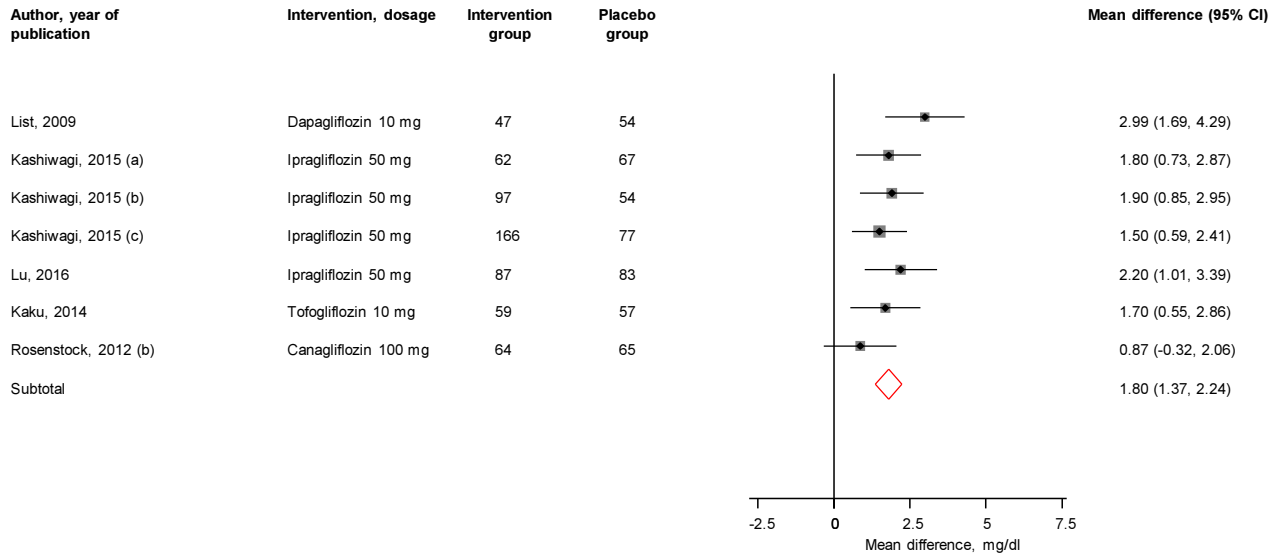
CI, confidence interval (bars); SGLT2, sodium–glucose co-transporter 2

Figure 3. Mean difference in estimated glomerular filtration levels comparing SGLT2 inhibition with placebo in populations without renal impairment, by class of SGLT2 inhibitor



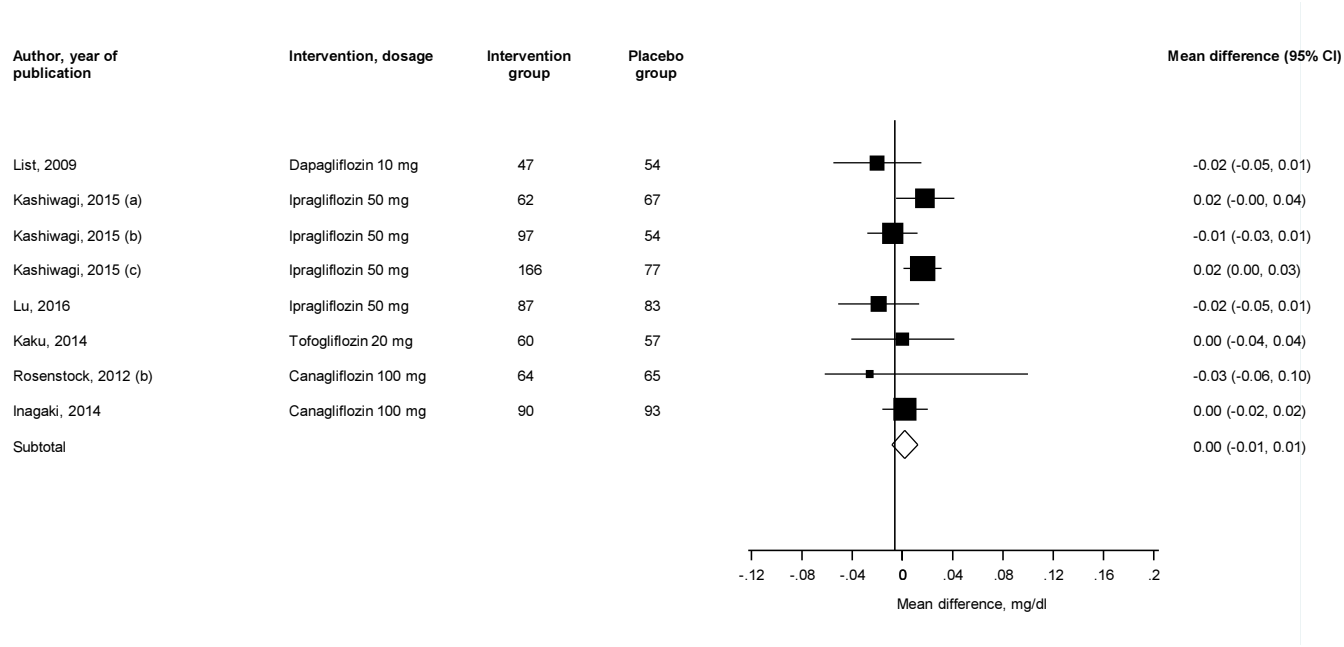
CI, confidence interval (bars); SGLT2, sodium–glucose co-transporter 2

Figure 4. Mean difference in BUN comparing SGLT2 inhibition with placebo in populations without renal impairment



BUN, blood urea nitrogen; CI, confidence interval (bars); SGLT2, sodium–glucose co-transporter 2

Figure 5. Mean difference in creatinine levels comparing SGLT2 inhibition with placebo in populations without renal impairment



CI, confidence interval (bars); SGLT2, sodium–glucose co-transporter 2

Table 1. Characteristics of clinical trials of SGLT2 inhibitors included in systematic review

Author, year of publication	Name of study	Study design	Patient population	Location	Baseline year of study	Age group (years)	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)
With renal impairment														
Yale, 2013; Yale, 2014	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control and stage 3 CKD	89 centres in 19 countries	NR	≥ 25	60.6	Unclear	Yes	Yes	Canagliflozin, 100 and 300 mg	26 (core period) 26 (extension period)	90/89	90
Barnett, 2014	EMPA-REG RENAL	Randomised, double-blind with placebo	T2DM and stage 3 CKD	127 centres in 15 countries	2010-2012	≥ 18	56.7	Adequate	Yes	Yes	Empagliflozin, 25 mg	52	187	187
Kohan, 2014	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control and estimated GFR 30 to 59 ml/min/1.73 m^2	111 sites in 13 countries	2008-2009	≥ 18	65.1	Unclear	Yes	Yes	Dapagliflozin, 5 and 10 mg	24 (short-term period) 28 (long-term period) 2nd year (extension period)	83/85	84
Kashiwagi, 2015	LANTERN	Randomised, double-blind with placebo	T2DM and estimated GFR 30 to 59 ml/min/1.73 m^2	Japan	2011-2012	20-74	78.0	Unclear	Yes	Yes	Ipragliflozin, 50 mg	24 (core period) 28 (extension period)	58	23
Wanner, 2016	EMPA-REG OUTCOME	Randomised, double-blind with placebo	T2DM and prevalent kidney disease	590 sites in 42 countries	2010-2013	≥ 18	67.8	Adequate	Yes	Yes	Empagliflozin, 10 or 25 mg	2.6 years	1,212	607
Haneda, 2016	-	Randomised, double-blind with placebo	T2DM and estimated GFR ≥ 30 to < 60 ml/min/1.73 m^2	Japan	NR	≥ 20	76.6	Adequate	Yes	Yes	Luseogliflozin, 2.5 mg	24 (core period) 28 (extension period)	95	50
With no renal impairment														
Wilding, 2009	-	Randomised, double-blind with placebo	T2DM poorly controlled with high insulin plus oral antidiabetic drugs	26 centres in US and Canada	2006-2007	18-75	59.2	Unclear	Yes	Yes	Dapagliflozin, 10 and 20 mg	12	24 / 24	23
List, 2009	-	Randomised, double-blind with placebo	T2DM	98 centres in US, 24 in Canada, 8 in Mexico, 3 in Puerto Rico	2005-2006	18-79	54.0	Unclear	Yes	Yes	Dapagliflozin, 2.5, 5, 10, 20, and 50 mg	12	59 / 58 / 47 / 59 / 56	54
Ferrannini, 2010	-	Randomised, double-blind with placebo	T2DM treatment naïve inadequately controlled with diet and exercise alone	85 centres in US, Canada, Mexico, Russia	2007-2008	18-77	48.2	Unclear	Yes	Yes	Dapagliflozin, 2.5, 5, and 10 mg	24	65 / 64 / 70	75
Bailey, 2010	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control on metformin therapy	80 sites	2007-2008	18-77	53.5	Adequate	Yes	Yes	Dapagliflozin, 2.5, 5, and 10 mg	24	137 / 135 / 135	137
Nauck, 2011	-	Randomised, double-blind with glipizide	T2DM inadequately controlled with metformin		2008	≥ 18	55.1	Adequate	Yes	Yes	Dapagliflozin, 2.5/5/10 mg	52	406	408

Author, year of publication	Name of study	Study design	Patient population	Location	Baseline year of study	Age group (years)	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)
Strojek, 2011	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control on glimepiride	84 sites	2008-2009	≥ 18	47.7	Adequate	Yes	Yes	Dapagliflozin, 2.5, 5, and 10 mg	24	154 / 145 / 151	146
Bolinder, 2012	-	Randomised, double-blind with placebo	T2DM	40 sites in 5 countries	2009	30-75	55.6	Adequate	Yes	Yes	Dapagliflozin, 10 mg	24	89	91
Rosenstock, 2012	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control on pioglitazone	105 sites	2008-2009	≥ 18	49.5	Unclear	Yes	Yes	Dapagliflozin, 5 and 10 mg	48	141 / 140	139
Rosenstock, 2012 (b)	-	Randomised, double-blind with placebo	T2DM inadequately controlled with metformin	85 sites in 12 countries	NR	18-65	52.0	Unclear	Yes	Yes	Canagliflozin, 50, 100, 200 and 300 mg	12	64 / 64 / 65 64	65
Stenlof, 2013	CANTATA-M	Randomised, double-blind with placebo	T2DM inadequately controlled with diet and exercise	17 countries	NR	18-80	44.2	Unclear	Yes	Yes	Canagliflozin, 100 and 300 mg	26	197 / 197	192
Lavalle-Gonzalez, 2013	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control on metformin therapy	169 centres in 22 countries	2010-2012	18-80	47.1	Adequate	Yes	Yes	Canagliflozin, 100 and 300 mg	52	296 / 295	139
Ferrannini, 2013	-	Randomised, double-blind with placebo	T2DM	75 centres in 13 countries	NR	18-79	52.0	Adequate	Yes	Yes	Empagliflozin, 5, 10, and 25 mg	12	81 / 81 / 82	82
Bode, 2013	-	Randomised, double-blind with placebo	T2DM with inadequate glycaemic control on glucose lowering agents	90 centres in 17 countries	2010-2011	55-80	55.5	Adequate	Yes	Yes	Canagliflozin, 100 and 300 mg	26	241 / 236	237
Cefalu, 2013	CANTATA-SU	Randomised, double-blind with glimepiride	T2DM with inadequate glycaemic control on glucose lowering agents	157 centres in 19 countries	2009-2011	18-80	52.0	Adequate	Yes	Yes	Canagliflozin, 100 and 300 mg	52	483 / 485	482
Wilding, 2013	CANTATA-MSU	Randomised, double-blind with placebo	T2DM inadequately controlled	85 centres in 11 countries	2010-2012	18-80	51.0	Adequate	Yes	Yes	Canagliflozin, 100 and 300 mg	52	157 / 156	156
Inagaki, 2014	-	Randomised, double-blind with placebo	T2DM	31 insitutions in Japan	2011-2012	≥ 20	70.5	Adequate	Yes	Yes	Canagliflozin, 100 and 200 mg	24	90 / 89	93
Kovacs, 2014	EMPA-REG PIO	Randomised, double-blind with placebo	T2DM	69 centres in 8 countries	NR	≥ 18	48.4	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	24	165 / 168	165
Ridderstrale, 2014	-	Randomised, double-blind with glimepiride	T2DM	173 sites in 23 countries	2010-2011	≥ 18	55.1	Adequate	Yes	Yes	Empagliflozin, 25 mg	104	765	780

Author, year of publication	Name of study	Study design	Patient population	Location	Baseline year of study	Age group (years)	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)
Haring, 2013; Haering, 2015	EMPA-REG METSU; EMPA-REG EXTEND METSU	Randomised, double-blind with placebo	T2DM inadequately controlled	149 centres in 12 countries	2010-2012	≥ 18	51.0	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	24 (core period) 52 (extension period)	226 / 218 225 / 216	225 225
Tikkanen, 2015	EMPA-REG BP	Randomised, double-blind with placebo	T2DM with hypertension	Finland	2011-2012	≥ 18	60.1	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	12	276	271
Haring, 2014	EMPA-REG MET	Randomised, double-blind with placebo	T2DM inadequately controlled	148 centres in 12 countries	2010-2012	≥ 18	57.0	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	24	217 / 213	207
Forst, 2014	-	Randomised, double-blind with placebo	T2DM inadequately controlled	74 centres in 11 countries	NR	18-80	63.2	Adequate	Yes	Yes	Canagliflozin, 100 and 300 mg	52	113 / 114	115
Kaku, 2014	-	Randomised, double-blind with placebo	T2DM inadequately controlled with diet/exercise alone	33 sites in Japan	2010-2012	20-74	65.1	Adequate	Yes	Yes	Tofogliflozin, 10, 20, and 40 mg	24	59 / 60 / 59	57
Kadowaki, 2014	-	Randomised, double-blind with placebo	T2DM	32 centres in Japan	NR	18-80	75.0	Adequate	Yes	Yes	Empagliflozin, 5 and 10 mg	12	110 / 109	109
Rosenstock, 2014	-	Randomised, double-blind with placebo	T2DM inadequately controlled and obese	104 centres in 14 countries	2011-2013	56.7*	45.0	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	52	186 / 189	188
Seino, 2014	-	Randomised, double-blind with placebo	T2DM	40 sites in Japan	2009	20-74	NR	Adequate	Yes	Yes	Luseogliflozin, 0.5, 2.5, and 5 mg	12	61 / 61 / 61	56
Seino, 2014 (b)	-	Randomised, double-blind with placebo	T2DM	41 sites in Japan	2010-2011	20-74	NR	Adequate	Yes	Yes	Luseogliflozin, 1, 2.5, 5, and 10 mg	12	56 / 56 / 54 / 58	58
Seino, 2014 (c)	-	Randomised, double-blind with placebo	T2DM	23 sites in Japan	2011-2012	≥ 20	73.4	Adequate	Yes	Yes	Luseogliflozin, 2.5 mg	24	79	79
Rosenstock, 2015	-	Randomised, double-blind with placebo	T2DM inadequately controlled on basal insulin	97 centres in 7 countries	2009-2012	58.8*	56.0	Adequate	Yes	Yes	Empagliflozin, 10 and 25 mg	78	169 / 155	170
Kashiwagi, 2015 (a)	BRIGHTEN	Randomised, double-blind with placebo	T2DM	22 sites in Japan	2010	NR	NR	Unclear	Yes	Yes	Ipragliflozin, 50 mg	16	62	67

Author, year of publication	Name of study	Study design	Patient population	Location	Baseline year of study	Age group (years)	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)
Kashiwagi, 2015 (b)	SPOTLIGHT	Randomised, double-blind with placebo	T2DM inadequately controlled	Japan	2010	≥ 20	73.7	Adequate	Yes	Yes	Ipragliflozin, 50 mg	24	97	54
Kashiwagi, 2015 (c)	EMIT	Randomised, double-blind with placebo	T2DM inadequately controlled	35 sites in Japan	2010-2012	≥ 20	NR	Adequate	Yes	Yes	Ipragliflozin, 50 mg	24	166	77
Lu, 2016	-	Randomised, double-blind with placebo	T2DM	30 sites in Korea and Taiwan	2011-2013	NR	NR	Adequate	Yes	Yes	Ipragliflozin, 50 mg	22	87	83
Neal, 2017	CANVAS Program	Randomised, double-blind with placebo	T2DM with high cardiovascular risk, estimated GFR > 30	667 centres in 30 countries	2009, 2014	≥ 30	64.2	Adequate	Yes	Yes	Canagliflozin, 100/300 mg	188.2	5,795	4,347

*, are mean ages; CANTATA-M, CANagliflozin Treatment And Trial Analysis– Monotherapy; CANTATA-MSU, CANagliflozin Treatment And Trial Analysis – Metformin plus SUlphonylurea; CANTATA-SU, CANagliflozin Treatment And Trial Analysis versus SUlphonylurea; CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; GFR, glomerular filtration rate; LANTERN, Long-Term ASP1941 Safety Evaluation in Patients with Type 2 Diabetes with Renal Impairment; NR, not reported; SGLT2, sodium–glucose co-transporter 2; T2DM, type 2 diabetes mellitus

Table 2. Results of changes in outcomes in relevant trials that could not be pooled

Author, year of publication	Name of study	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)	Change in treatment arm	Change in placebo arm
Estimated glomerular filtration rate – populations without renal impairment							
Wilding, 2009	-	Dapagliflozin, 10 mg	12	24	23	Mean change (-0.840) ml/min/1.73 m²	Mean change (-0.580) ml/min/1.73 m²
		Dapagliflozin, 20 mg		24	23	Mean change (1.450) ml/min/1.73 m²	Mean change (-0.580) ml/min/1.73 m²
Nauck, 2011	-	Dapagliflozin, 2.5/5/10 mg	52	406	Glipizide arm (408)	Mean (SE) change: -0.50 (0.80) ml/min/1.73 m²	Mean (SE) change: -5.40 (0.80) ml/min/1.73 m²
Cefalu, 2013	CANTATA-SU	Canagliflozin, 100 mg	52	483	Glimepiride 482	Mean change (-1.70) ml/min/1.73 m²	Mean change (-5.10) ml/min/1.73 m²
		Canagliflozin, 300 mg		485	Glimepiride 482	Mean change (-3.00) ml/min/1.73 m²	Mean change (-5.10) ml/min/1.73 m²
Blood urea nitrogen – populations without renal impairment							
Cefalu, 2013	CANTATA-SU	Canagliflozin, 100 mg	52	483	Glimepiride 482	Mean (SD) percent change: 15.30 (29.10)	Mean (SD) percent change: 6.50 (26.40)
		Canagliflozin, 300 mg		485	Glimepiride 482	Mean (SD) percent change: 22.00 (30.80)	Mean (SD) percent change: 6.50 (26.40)
Seino, 2014 (b)	-	Luseogliflozin, 1 mg	12	56	58	Least squares mean change: 1.6 (95% CI, 0.8-2.4) mg/dl	Least squares mean change: 0.4 (95% CI, -0.4-1.2) mg/dl
		Luseogliflozin 2.5 mg		56	58	Least squares mean change: 0.9 (95% CI, 0.1-1.7) mg/dl	Least squares mean change: 0.4 (95% CI, -0.4-1.2) mg/dl
		Luseogliflozin, 5 mg		54	58	Least squares mean change: 1.4 (95% CI, 0.6-2.2) mg/dl	Least squares mean change: 0.4 (95% CI, -0.4-1.2) mg/dl
		Luseogliflozin, 10 mg		58	58	Least squares mean change: 1.6 (95% CI, 0.8-2.4) mg/dl	Least squares mean change: 0.4 (95% CI, -0.4-1.2) mg/dl
Seino, 2014 (c)	-	Luseogliflozin 2.5 mg	24	79	79	Least squares mean difference: 1.80 (95% CI, 0.80-2.80) mg/dl	
Nauck, 2011	-	Dapagliflozin, 2.5/5/10 mg	52	406	Glipizide arm (408)	Mean (SE) change: -0.50 (0.80) mmol/l	Mean (SE) change: 0.10 (0.07) mmol/l
Serum creatinine – populations without renal impairment							

Author, year of publication	Name of study	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)	Change in treatment arm	Change in placebo arm
Seino, 2014		Luseogliflozin, 0.5 mg	12	61	56	Least squares mean change: -0.002 (95% CI, -0.02, 0.01) mg/dl	Least squares mean change: -0.004 (95% CI, -0.02, 0.01) mg/dl
		Luseogliflozin 2.5 mg		61	56	Least squares mean change: 0.003 (95% CI, -0.01, 0.02) mg/dl	Least squares mean change: -0.004 (95% CI, -0.02, 0.01) mg/dl
		Luseogliflozin, 5 mg		61	56	Least squares mean change: 0.012 (95% CI, 0.00, 0.03) mg/dl	Least squares mean change: -0.004 (95% CI, -0.02, 0.01) mg/dl
Seino, 2014 (b)	-	Luseogliflozin, 1 mg	12	56	58	Least squares mean change: -0.021 (95% CI, -0.037, -0.005) mg/dl	Least squares mean change: -0.005 (95% CI, -0.02, 0.011) mg/dl
		Luseogliflozin 2.5 mg		56	58	Least squares mean change: -0.005 (95% CI, -0.021, 0.011) mg/dl	Least squares mean change: -0.005 (95% CI, -0.02, 0.011) mg/dl
		Luseogliflozin, 5 mg		54	58	Least squares mean change: 0.011 (95% CI, -0.005, 0.027) mg/dl	Least squares mean change: -0.005 (95% CI, -0.02, 0.011) mg/dl
		Luseogliflozin, 10 mg		58	58	Least squares mean change: 0.009 (95% CI, -0.007, 0.025) mg/dl	Least squares mean change: -0.005 (95% CI, -0.02, 0.011) mg/dl
Seino, 2014 (c)	-	Luseogliflozin 2.5 mg	24	79	79	Least squares mean difference: -0.001 (95% CI, -0.021, 0.018) mg/dl	
Nauck, 2011	-	Dapagliflozin, 2.5/5/10 mg	52	406	Glipizide arm (408)	Mean (SE) change: -0.180 (1.110) µmol/l	Mean (SE) change: 3.620 (0.630) µmol/l
Ridderstrale, 2014	-	Empagliflozin, 25 mg	104	765	Glimepiride arm (780)	Mean (SD) change: 0.00 (13.00) µmol/l	Mean (SD) change: 2.00 (9.00) µmol/l
Urine albumin-to-creatinine ratio – populations with renal impairment							
Yale, 2013	-	Canagliflozin, 100 mg	26	90	90	Median percent change (-29.9)	Median percent change (-7.5)
		Canagliflozin 300 mg		89	90	Median percent change (-20.9)	Median percent change (-7.5)
Yale, 2014	-	Canagliflozin 100 mg	52	90	90	Median percent change (-16.4)	Median percentage change (19.7)
		Canagliflozin 300 mg		89	90	Median percent change (-28.0)	Median percent change (19.7)

Author, year of publication	Name of study	Medication and dosage	Duration of therapy (weeks)	Treatment arm (N)	Placebo arm (N)	Change in treatment arm	Change in placebo arm
Kohan, 2014	-	Dapagliflozin 5 mg	104	83	84	Mean (SE) change: 78 (112.5) mg/g	Mean (SE) change: 69.7 (80.1) mg/g
		Dapagliflozin 10 mg		85	84	Mean (SE) change: -11.69 (148.6) mg/g	Mean (SE) change: 69.7 (80.1) mg/g
Kashiwagi, 2015	LANTERN	Ipragliflozin, 50 mg	24	58	23	Mean (SD) change: -37.1 (279.14) mg/g Cr	Mean (SD) change: 18.08 (82.196) mg/g Cr
Barnett, 2014	EMPA-REG RENAL	Empagliflozin, 25 mg	52	187	187	Adjusted mean difference comparing empagliflozin with placebo: -183.78; 95% CI: -305.18, -62.38; *p*=0.0031	
Urine albumin-to-creatinine ratio – populations without renal impairment							
Ferrannini, 2013	-	Empagliflozin, 5 mg	12	81	82	Median change (-0.340) mg/mmol	Median change (-0.780) mg/mmol
		Empagliflozin, 10 mg		81	82	Median change (-0.360) mg/mmol	Median change (-0.780) mg/mmol
		Empagliflozin, 25 mg		82	82	Median change (-1.00) mg/mmol	Median change (-0.780) mg/mmol
Cefalu, 2013	CANTATA-SU	Canagliflozin, 100 mg	52	483	Glimepiride 482	Mean (SE) change: -0.10 (4.70) g/mol	Mean (SE) change: 0.70 (15.30) g/mol
		Canagliflozin, 300 mg		485	Glimepiride 482	Mean (SE) change: -0.90 (6.70) g/mol	Mean (SE) change: 0.70 (15.30) g/mol
Nauck, 2011	-	Dapagliflozin, 2.5/5/10 mg	52	406	Glipizide arm (408)	Mean (SE) change: -19.00 (6.60) mg/g	Mean (SE) change: -0.80 (7.10) mg/g
Ridderstrale, 2014	-	Empagliflozin, 25 mg	104	765	Glimepiride arm (780)	Mean (SD) change: 6.70 (37.70) mg/g	Mean (SD) change: 8.60 (72.60) mg/g
Urine albumin-to-creatinine ratio – populations with renal impairment							
Ridderstrale, 2014	-	Empagliflozin, 25 mg	16	19	Glimepiride arm (780)	Mean (SD) change: -483.5 (613.7) mg/g	Mean (SD) change: 380.1 (1161.5) mg/g

CANTATA-SU, CANagliflozin Treatment And Trial Analysis versus SUlphonylurea; LANTERN, Long-Term ASP1941 Safety Evaluation in Patients with Type 2 Diabetes with Renal Impairment; SD, standard deviation; SE, standard error

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MEDLINE literature search strategy
Appendix 3	Assessment of risk of bias

Appendix 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figures 2-4;
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			

Section/topic	Item No	Checklist item	Reported on page No
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Page 18

Appendix 2: MEDLINE literature search strategy

Relevant studies published from inception to March 06, 2017 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), and by hand searching of relevant journals. The computer-based searches combined terms related to the intervention (e.g., *SGLT2 inhibitors, dapagliflozin, canagliflozin, empagliflozin*); population (e.g., *type 2 diabetes, renal impairment, CKD, renal insufficiency*); and outcomes (e.g., *serum creatinine, urine albumin-to-creatinine ratio*) in humans, without any language restriction.

1 exp Canagliflozin/ (259)
2 dapagliflozin.mp. (443)
3 empagliflozin.mp. (437)
4 exp Sodium-Glucose Transporter 2/ (904)
5 SGLT inhibitor.mp. (37)
6 exp Sodium-Glucose Transport Proteins/ (1865)
7 sodium glucose-cotransporter.mp. (834)
8 exp Diabetes Mellitus, Type 2/ (106242)
9 exp Diabetes Mellitus/ (364281)
10 diabetes.mp. (501764)
11 exp Renal Insufficiency, Chronic/ (97154)
12 exp Kidney Failure, Chronic/ (85142)
13 exp Renal Insufficiency/ (146319)
14 exp Kidney Diseases/ (459420)
15 chronic renal insufficiency.mp. (4627)
16 impaired kidney function.mp. (623)
17 decreased kidney function.mp. (296)
18 decreased renal function.mp. (927)
19 exp Glomerular Filtration Rate/ (37580)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 (2662)
21 8 or 9 or 10 (531039)
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (478834)
23 20 and 21 and 22 (151)
24 limit 23 to humans (119)

Each part was specifically translated for searching alternative databases.

Appendix 3: Assessment of risk of bias

No.	Trials	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
1	Yale, 2013 and 2014	+	?	+	+	+	+	+
2	Barnett, 2014	+	+	+	+	+	+	+
3	Kohan, 2014	+	?	+	+	+	+	+
4	Kashiwagi, 2015	+	?	+	+	+	+	+
5	Wanner, 2016	+	+	+	+	?	?	?
6	Haneda, 2016	+	+	+	+	+	+	+
7	Wilding, 2009	+	?	+	?	?	?	?
8	List, 2009	+	?	+	?	+	+	+
9	Ferrannini, 2010	+	?	+	?	+	+	+
10	Bailey, 2010	+	+	+	?	+	+	+
11	Nauck, 2011	+	+	+	?	+	+	+
12	Strojek, 2011	+	+	+	?	+	+	+
13	Bolinder, 2012	+	+	+	?	+	+	+
14	Rosenstock, 2012	+	?	+	?	?	?	?
15	Rosenstock, 2012 (b)	+	?	+	?	?	?	?
16	Stenlof, 2013	+	?	+	?	?	?	?
17	Lavalle-Gonzalez, 2013	+	+	+	?	+	+	+
18	Ferrannini, 2013	+	+	+	?	?	?	?
19	Bode, 2013	+	+	+	?	+	+	+
20	Cefalu, 2013	+	+	+	?	+	+	+
21	Wilding, 2013	+	+	+	?	+	+	+
22	Inagaki, 2014	+	+	+	?	?	?	?
23	Kovacs, 2014	+	+	+	?	?	?	?
24	Ridderstrale, 2014	+	+	+	?	+	+	+
25	Haring, 2013; Haering, 2015	+	+	+	?	?	?	?
26	Tikkanen, 2015	+	+	+	?	?	?	?
27	Haring, 2014	+	+	+	?	?	?	?
28	Forst, 2014	+	+	+	?	+	+	+
29	Kaku, 2014	+	+	+	+	+	+	+
30	Kadowaki, 2014	+	+	+	?	?	?	?
31	Rosenstock, 2014	+	+	+	?	?	?	?
32	Seino, 2014	+	+	+	?	?	?	?
33	Seino, 2014 (b)	+	+	+	?	?	?	?
34	Seino, 2014 (c)	+	+	+	+	?	?	?
35	Rosenstock, 2015	+	+	+	?	?	?	?
36	Kashiwagi, 2015 (a)	+	?	+	?	+	+	+
37	Kashiwagi, 2015 (b)	+	+	+	?	+	+	+
38	Kashiwagi, 2015 (c)	+	+	+	?	+	+	+
39	Lu, 2016	+	+	+	?	+	+	+
40	Neal, 2017	+	+	+	+	?	?	?

+	Low risk of bias
?	Unclear risk of bias
-	High risk of bias